UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,488	07/05/2001	Barry John Langham	CELL-0113	2595

7590 07/24/2002

Woodcock Washburn Kurtz
Mackiewicz & Norris LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103

EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/899,488	Applicant(s) LANGHAM ET AL.	
	Examiner Thomas McKenzie Ph.D.	Art Unit 1624	

-- The MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 7/5/01. There are twenty-six claims pending and twenty-six under consideration. Claims 1-19 are compound claims. Claim 20 is a composition claim. Claims 22-26 are use claims. Claim 21 appears to be a compound claim. This is the first action on the merits. The application concerns some cyclobut-3-en-1,2-dione compounds, compositions, and uses thereof.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 and 20-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a linker atom or group" defining L^1, L^2, L^3, and L^4 is indefinite. The term is defined in lines 12-20, page 8 using open language. What else is intended here?

3. Claims 1, 2, 5-18, and 20-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "derivative" in line 4, page 51 is indefinite for we do not know which compounds are contemplated. A derivative is the result of a reaction upon an organic

molecule. Since we do not know the reagents or the conditions of these reactions, there is no way of determining the structures of the claimed "derivative". The word is, in essence, a product by process claim. Yet, Applicants have not described the intended processes sufficiently that we may understand the structures of the compounds they claim. Webster's New World Dictionary defines derivative as "a substance derived from ... another substance by chemical change", and "substitution of one or more elements or radicals for one or more constituents of the original substance" has occurred. All implying that new chemical bonds have formed. Both aldehydes and alcohols are derivatives of an acid. Complete reduction or decarboxylation of a carboxylic acid will give a methyl group or a hydrogen atom respectively. Are these four groups derivatives?

4. The phrase "biostere thereof" is indefinite. The term is defined in lines 23-26, page 11 using open language. What else is intended? The prefix "bio" implies that the acid derivative is biologically active. What if it is not? Must it be as active as the acid to be a "biostere"?

5. Claims 1-12, 14-18, and 20-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The words, in lines 11 and 12, page 51 "cycloaliphatic", "heteocycloaliphatic",

polycycloaliphatic" and "heteropolycyclo-aliphatic" are indefinite. Firstly, while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The sole requirement for an aliphatic group is that it lacks rings. Thus, "cycloaliphatic" is an oxymoron. The examples of such groups Applicants provide in lines 16-21, page 15 are cycloalkyl groups. Is this what is intended?

Secondly, is heterocycloaliphatic an aliphatic substituted by a heterocycle, e.g. pyridyl-methyl? A cycloalkyl interrupted by a heteroatom, such as piperidinyl? A cycloalkyl substituted by a heteroatom, e.g. chlorocyclohexyl? Applicants' examples in lines 23-28, page 15 do not clarify the issue and define the term in terms of itself. Furthermore, in lines 9-15, page 9 Applicants offer piperidinyl as an example of a "heterocyclic ring", implying that a "heterocycloaliphatic" must be something different.

6. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "particularly" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

7. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a disease or disorder *** leukocytes plays a role" is indefinite. In addition to the diseases listed in the dependant claims, what other treatments are being claimed?

8. Claims 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These are use claims, yet depend upon a compound claim.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the salts and N-oxides of the claimed compounds, does not reasonably provide enablement for making "solvates" or "hydrates" of the claimed compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are two grounds for making this rejection. Firstly, what solvents are contemplated for making the "solvates"?

Secondly, the claims are drawn to solvates and hydrates. However, the numerous examples presented in the nine examples spanning pages 42-45 all failed to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. It is unpredictable whether a particular solvent or water will form a solvate or hydrate with a particular host molecule. The Examiner suggests deleting the two words.

10. Claims 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific diseases, does not reasonably provide enablement for "prophylaxis" of any disease. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The only established prophylactics are vaccines not the squaric acid. analogs such as present here. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of inflammatory diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. In addition, it is presumed that prevention of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. The Examiner suggests deletion of the word "prophylaxis".

11. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. Since the phrase "a disease or disorder *** leukocytes plays a role" is not defined in the specification and is not art-recognized, how is the skilled physician to understand what diseases are to be treated?

12. Claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the other listed diseases of claim 22, does not reasonably provide enablement for treating multiple sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Polman (BMJ) reports in the table on page 492 that interferon is the only established therapy for multiple sclerosis. Glatiramer acetate is a second line treatment used in the US but not Europe. Cohen (J. Neuroimmun.) in Table 3 on page 30 states that the only available treatment options for multiple sclerosis are interferon (rlFNβ), Glatiramer acetate (GA), the steroid methylprednisolone (IVMP), the immunesuppresives azathioprine (AZA), methotrexate (MTX), and cyclophosphamide (CTX), and immunglobin (IVIg). Cell adhesion inhibitors are not presently art-recognized to be efficacious for this purpose. Thus, the skilled clinician would not know how to use them to treat MS with Applicants' compounds. Case law is clear on this point. In an unpredictable

art, such as MS therapy, models may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

13. Claims 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. This claim would read on α4 integrin binding inhibition in mammals with below normal α4 integrin binding activity, α4 integrin binding inhibition in mammals with normal α4 integrin binding activity, or in asymptomatic mammals with up-regulated α4 integrin binding activity. The specification fails to teach any benefit to be gained from such actions.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A

timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14 and 20-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-6, 9, and 10 of copending Application No. 09/579,317. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 1 of 09/579,317 claims "Het" as "naphthyridinyl" generally. Applicants' provisos in the last three lines of the present claim 1 exclude two specific naphthyridinyl rings with two specific attachment points. There are other naphthyridinyl rings and other attachment points not excluded by this proviso. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-26 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/742,038. Although the conflicting claims are not

identical, they are not patentably distinct from each other because claim 1 of 09/742,038 is drawn to heteroaromatic rings generally. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Applicants are reminded of the MPEP§2001.06(b) "Information Relating to or From Copending United States Patent Applications. The individuals covered by 37 CFR 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications which are "material to patentability" of the application in question. As set forth by the court in *Armour & Co. v. Swift & Co.*, 466 F.2d 767, 779, 175 USPQ 70, 79 (7th Cir. 1972):

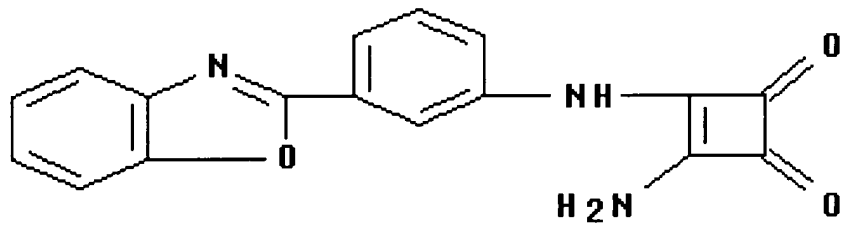
> [W]e think that it is unfair to the busy examiner, no matter how diligent and well informed he may be, to assume that he retains details of every pending file in his mind when he is reviewing a particular application . . . [T]he applicant has the burden of presenting the examiner with a complete and accurate record to support the allowance of letters patent.

See also MPEP § 2004, paragraph 9. Accordingly, the individuals covered by 37 CFR 1.56 cannot assume that the examiner of a particular application is necessarily aware of other applications which are "material to patentability" of the application in question, but must instead bring such other applications to the attention of the examiner. For example, if a particular inventor has different applications pending

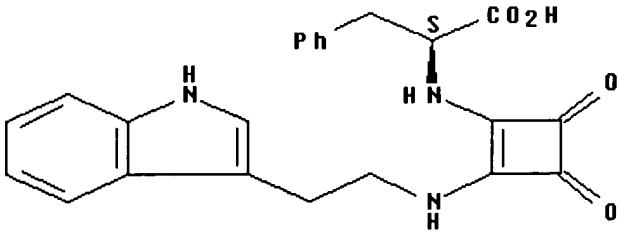
in which similar subject matter but patentably indistinct claims are present that fact must be disclosed to the examiner of each of the involved applications."

Allowable Subject Matter

17. Applicants' compounds are novel over both Pamukcu ('220) and Coates (WO 94/29277 A1) who teach the compound shown below, possessing Applicants required "Het" ring but lacking Applicants required carboxylic acid group.



Applicants' compounds are novel over Lombardo (ref HU), which teaches the compound shown below with the isomeric point of attachment to the "Het" ring but with the carboxylic acid attached to a different "Alk" group.



Conclusion

18. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final

amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mark Berch
Primary Patent Examiner
Art Unit 1624

TCMcK
July 17, 2002

DR MCKENZIE 麥金文博士